

# America's pharmaceutical research companies: Keeping the cost of health care down

Pharmaceutical Manufacturers Association

*A response to the staff report of the U.S. Senate Special Committee on Aging.*

The staff of the U.S. Senate Special Committee on Aging issued a report on September 24, 1991 intended for informational purposes. "It does not represent either findings or recommendations formally adopted by the Committee," according to the report.

The report is critical of America's pharmaceutical research companies on 5 principal points: prices, profits, marketing, research and tax credits.

The staff report is biased and replete with factual errors, erroneous interpretations and misstatements. Then, on the basis of flawed findings, the report presents misguided policy options.

America's pharmaceutical industry leads the rest of the world in innovation; the new drugs that are developed by the industry improve the health and quality of life of patients here and around the world. These medicines save lives and money. They often cure or control deadly diseases, shorten hospital stays, reduce physician visits and obviate surgery in millions of cases. Prescription medicines help hold down health-care costs. And they are the best hope for containing health-care costs in the future.

The following addresses the report's principal allegations.

## **Prescription drug prices/profitability**

Costs of discovering and developing pharmaceuticals have risen sharply.

- Industry-funded research and development expenditures have doubled every 5 years since 1970, reaching \$9.2 billion in 1991 — more than the total invested in biomedical research by all the National Institutes of Health.
- Drug prices have not risen as fast as the industry's R&D expenditures. In 1990, for example, the rise in pharmaceutical research was virtually double the rate of drug price increases across the industry.

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- Compared with all other U.S. industries, the pharmaceutical industry devotes a higher percentage of sales revenues to R&D — 16.5% in 1990 for all PMA member companies. This is more than 4 times the average of all industries.
- The latest estimate — by economists at Tufts University — of the cost of developing a new drug is \$231 million, up sharply from earlier estimates.
- A recent study by Duke University economist Henry Grabowski found that only 3 of every 10 drugs introduced by the pharmaceutical industry between 1970 and 1979 subsequently recovered their R&D costs.
- The Grabowski study also concluded that if prices had risen at only the general rate of inflation since 1980, the industry could not have recovered its costs for this portfolio of drugs and R&D expenditures would have been adversely affected.

The 1980s have seen greatly shortened product life cycles for pharmaceuticals.

- In 1984, the life cycle of pharmaceutical products that had lost patent protection was shortened dramatically with the passage of the Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch), which made possible quick approval of generic copies of brand-name products. Within 2 years of patent expiration, the typical pharmaceutical product now loses half of its market. This has put significant pressure on prices.

Foreign patent piracy raises costs.

- Countries such as India, Brazil and Thailand steal an estimated \$4.8 billion in patented inventions from U.S. pharmaceutical companies each year, according to the U.S. Trade Representatives and the International Trade Commission.

A different Consumer Price Index (CPI) base year would lead to different conclusions.

- To demonstrate that pharmaceutical price increases are advancing faster than other medical expenditures, the report uses 1980 as a base year. If the report had gone back to the CPI's previous base year of 1967, it would show that drug prices lagged behind the all-items CPI until 1990 — and still trails the CPI's medical component by 200 points. (See chart.)

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- Regardless of what the report implies, the average cost of a prescription drug in the U.S. in 1990 was \$19.94.

#### U.S. versus Canadian prices.

- Canadian prescription-drug prices vary from province to province, depending on many factors. Ontario, for example, will pay for only the cheapest generic drugs for its elderly and indigent residents. A similar approach for Medicaid was proposed by Senator Pryor last year and soundly rejected.
- Canada is the only Western industrialized nation that links the market exclusivity of a patented product to its price. Adopting such a patent-crippling system in the United States would have the same effect in this country as Canada's traditionally weak patent system has had in Canada. It would impair the U.S. pharmaceutical industry's innovativeness, making it far less competitive with drug industries in other industrialized countries, such as the United States, Japan, Germany and Switzerland, where patent laws are strong.
- The staff report fails to mention that Canada is the major industrial country with the weakest condition for pharmaceutical innovations, having contributed the least number of new compounds in recent years to cure diseases. Those who advocate Canada's system of price controls and weak patent protection invite a rapid decline in American pharmaceutical innovation, with disastrous consequences for the health of our citizens.

#### Pharmaceutical industry profitability

- Investments in high-risk ventures — such as new drug development, where fewer than 1 in 5,000 chemicals or biologicals tested actually is ever marketed — appropriately require a rate of return considerably higher than could be obtained from placing the same money in an average company.

#### Pharmaceutical industry marketing

##### Marketing practices conform to AMA guidelines

- The staff report's examples of "abusive marketing and promotional practices" do not reflect today's market. Pharmaceutical promotional practices conform to guidelines adopted by the American Medical Association's House of Delegates on December 4, 1990, which the PMA Board of Directors adopted 2 days later. Since the guidelines forbid the practices cited in the report, legislative remedies are unnecessary.

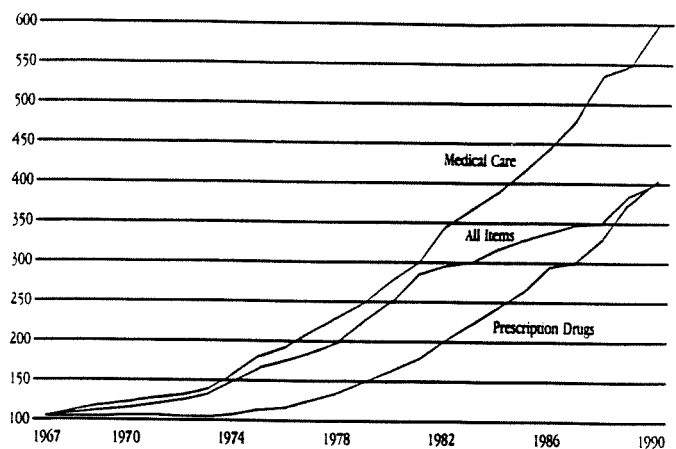
#### Pharmaceutical industry research

##### Drug industry breakthrough research

- The report asserts that "few breakthrough drugs" have resulted from the drug industry pricing policies that have sustained research and development. This ignores dozens of "break-through" drugs in past decades. They include biotechnology breakthroughs such as human growth hormone for dwarfism, interferon alpha for AIDS-related Kaposi's sarcoma, erythropoietin for dialysis-associated anemia and granulocyte colony

#### Rx Drug Prices Below Other Indices

Consumer Price Indexes 1967-1989



Source: Bureau of Labor Statistics

stimulating factor for chemotherapy-induced neutropenia (low white blood cell count). It flagrantly ignores the many breakthrough "conventional" drugs and vaccines for diseases such as river blindness, African sleeping sickness, malaria, severe combined immunodeficiency disease (the so-called "Bubble Boy" disease), AIDS-associated cytomegalovirus retinitis, AIDS-associated cryptococcal meningitis and systemic candidal infections, hepatitis B, haemophilus influenza type B, and neonatal respiratory distress syndrome. And the R&D pipeline is bursting with future breakthroughs.

- The report shows little appreciation of the value of the second or third products on the market in a therapeutic category. These products, though perhaps not breakthroughs, often offer major advances in treatment and reduction in side effects. Examples include newer cephalosporin antibiotics requiring less frequent administration and enabling home intravenous use; improved cancer chemotherapeutic agents which eliminate hospitalization, and newer medications effective in the treatment of schizophrenia and depression.

#### There are better ways to lower cost of providing needed medicines

Policy options which might actually help reduce the cost of prescription drugs are:

- *Streamline the drug approval process.* The average cost of getting a drug onto the U.S. market could be cut substantially if clinical testing and FDA review times were reduced to that experienced in major European countries such as the United Kingdom.
- *Reduce patent piracy.* U.S. research-based pharmaceutical companies lose about \$5 billion a year to international patent pirates, who copy their drugs without per-

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# AXID<sup>®</sup> nizatidine capsules

**Brief Summary.** Consult the package insert for complete prescribing information.

**Indications and Usage:** 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

**Contraindication:** Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H<sub>2</sub>-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H<sub>2</sub>-receptor antagonists.

**Precautions:** General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

**Laboratory Tests**—False-positive tests for urobilinogen with Multistix<sup>®</sup> may occur during therapy.

**Drug Interactions**—No interactions have been observed with theophylline, chloridazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

**Pregnancy—Teratogenic Effects—Pregnancy Category C**—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**—Safety and effectiveness in children have not been established.

**Use in Elderly Patients**—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

**Adverse Reactions:** Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

**Hepatic**—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since marker introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

**Cardiovascular**—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

**CNS**—Rare cases of reversible mental confusion have been reported.

**Endocrine**—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

**Hematologic**—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H<sub>2</sub>-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

**Integumental**—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

**Hypersensitivity**—As with other H<sub>2</sub>-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

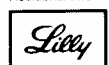
**Other**—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

**Overdosage:** Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

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Additional information available to the profession on request.



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## HEREDITARY ANEMIA (Continued from page 17)

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## PHARMACEUTICAL (Continued from page 16)

mission. Intellectual property protection must be strengthened, not weakened as in Canada, and tough action taken against patent pirates.

- **Cut product liability costs.** The high cost of protecting against the possibility of high jury awards in product liability cases adds millions of dollars to drug costs. A reform of the tort laws is needed, including protection against punitive damages for products that have been deemed safe and effective by the Food and Drug Administration.

### Conclusion

The Senate Aging Committee's staff is singling out one competitive industry for price controls and weakened patent protection. If their recommendations are enacted, it would have a damaging effect on both health care and U.S. international competitiveness.

